Methods-Instrumental variable

An 'instrument' is an observable variable used to simulate a coin-flip in assigning patients to treatment groups. Hence, IVs should not be related to health outcomes, except to the extent that they influence treatment assignment. The idea is that the effect of an exposure can be estimated without bias due to measured or unmeasured confounders through use of an IV that is related to exposure, but not related to outcome except through its relationship to exposure (1,2). The use of IVs in epidemiology has traditionally been limited because of a lack of strong IVs (3). Recently several investigators have suggested using individual physician factors such as prescriber preference as instruments in settings in which there is thought to be strong prescriber preference for different treatments under study (4-7).

IV was defined to be the proportion of patients treated at the NHC center using HBO. We used the two stage residual inclusion method to estimate the effect of HBO on outcome (8). The first model (a logistic regression model) examined the association between exposure (e.g. treatment assignment) as the dependent variable and the IV as the independent variable, controlling for baseline covariates such as age, sex, wound age, wound size, Wagner wound grade ≥2, the number of wounds on the patient, history of neuropathy, history of wound recurrence, and history of osteomyelitis or abscess. In the second stage we used Cox proportional hazards regression to model the outcome of either a healed wound or lower extremity amputation. This model included the treatment variable (HBO), the residuals (i.e., differences between predicted and observed responses) from the first stage model, and covariates. We assessed the strength of our IV on the basis of the F-statistic. Conventionally, F statistic values of <10 indicate weak instruments. We also evaluated the validity and plausibility of the IV by assessing its independence from the outcome (except through the treatment variable) and its association with important measured covariates by examining means and frequencies of observed covariates across levels of the IV.

Results- Instrumental Variable

We also evaluated the effectiveness of HBO using IV models. We selected the NHC center-based proportion treated with HBO as the IV. The mean proportion of individuals receiving HBO for any reason by center was 0.088 ± 0.057 (range from: 0.001 to 0.75). The F-statistic for the IV was 343.71 (expectation >10). Using the two-stage residual inclusion model, individuals receiving HBO therapy (Table 1s) were more likely to have a lower limb amputation (HR=3.03 (95% CI:1.69, 5.42)) and were less likely to heal (0.43 (0.35, 0.52)) than those who did not receive HBO therapy. This estimate did not change when the analysis was adjusted for potential confounders (see methods), when it was limited to those who were new to the NHC center, or when the outcome was determined after 6 weeks of care. If our study population was limited to just those who had wounds Wagner 3 or higher, then those who received HBO therapy were not significantly different from those who did not receive this therapy (Table 4).

Among those that received HBO, a median of 29 (25 to 75%;15 to 48) treatments were received. It is important to note that those who received HBO received their LEAs about three weeks later than those who did not (p=0.02). On average, amputations occurred at 88.6 ± 90.1 days for those who did not receive HBO versus 106.1 days ± 113.2 for those who received HBO. The location of the amputation also differed between recipients and non-recipients of HBO therapy. Those receiving HBO were more likely to have a major amputation (trans-tibial and higher) ((2.30 (1.18, 4.47) based on instrumental variable residual model (IVR) as compared to those who did not have a major outcome. Finally, if an assumption was made to insure patient treatment acceptance that an individual must have received at least 8 treatments (almost two weeks) with HBO in order to be considered treated with HBO then the effect of HBO
was less clear with respect to amputation ((1.24 (0.86, 1.79)) and with respect to a healed wound ((0.90 (0.80, 1.01))). The location of the amputation also differed between recipients and non-recipients of HBO therapy. Those receiving HBO were more likely to have a major amputation (trans-tibial and higher) ((2.30 (1.18, 4.47) based on instrumental variable residual model (IVR) as compared to those who did not have a major outcome. Finally, if an assumption was made to insure patient treatment acceptance that an individual must have received at least 8 treatments (almost two weeks) with HBO in order to be considered treated with HBO then the effect of HBO was less clear with respect to amputation ((1.24 (0.86, 1.79)) and with respect to a healed wound ((0.90 (0.80, 1.01))).

References


**Table 1s:** Hazard ratios for the effectiveness of HBO versus conventional care using an instrumental variable approach. All analyses were performed using proportional hazards model. Adjusted model included the covariates age, sex, wound age, wound size, Wagner wound grade ≥2, the number of wounds on the patient, history of neuropathy, history of wound recurrence, and history of osteomyelitis or abscess.

<table>
<thead>
<tr>
<th></th>
<th>Primary analysis</th>
<th>Fully adjusted</th>
<th>Limited to new subjects</th>
<th>Outcome by week six</th>
<th>Limited to those with Wagner grade 3 or greater wounds</th>
<th>Outcome</th>
<th>amputation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amputation</td>
<td>3.03 (1.69, 5.42)</td>
<td>2.40 (1.28, 4.52)</td>
<td>4.85 (2.17, 10.82)</td>
<td>3.24 (1.48, 7.07)</td>
<td>1.28 (0.50, 0.32)</td>
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<tr>
<td>Healed</td>
<td>0.43 (0.35, 0.52)</td>
<td>0.34 (0.28, 0.42)</td>
<td>0.44 (0.33, 0.58)</td>
<td>0.36 (0.27, 0.47)</td>
<td>0.94 (0.60, 1.46)</td>
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